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**Articles**

## Inhibition of Atherosclerosis Development in Cholesterol-Fed Human Apolipoprotein A-I- Transgenic Rabbits

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### ► Abstract

**Background** Prospective epidemiological studies support the hypothesis that high levels of high-density lipoprotein (HDL) cholesterol and apolipoprotein (apo) A-I limit atherosclerosis development. However, more data from studies with animal models of atherosclerosis that resemble the human disease are required to demonstrate the effect of apo A-I in the inhibition of atherogenesis. The rabbit is a good animal model for human atherosclerosis.

**Methods and Results** Human apo A-I-transgenic rabbits have been produced, and we have

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evaluated the effect of apo A-I on the development of atherosclerosis in transgenic rabbits fed a cholesterol-rich diet for 14 weeks. Plasma cholesterol levels of atherogenic apo B-containing lipoproteins were similar for transgenic and control rabbits ( $>1000$  mg/dL), while plasma levels of HDL cholesterol in the transgenic group were always about twice that of the control group ( $68 \pm 11$  versus  $37 \pm 3$  mg/dL at 14 weeks;  $P < .001$ ). At the end of the experiment, the amount of aortic surface area covered by lesions as well as the amount of lipid accumulation in the aorta were significantly less in transgenic rabbits compared with the control group ( $15 \pm 12\%$  versus  $30 \pm 8\%$ ,  $P < .0027$  for the surface area of the thoracic aorta;  $116 \pm 31$  versus  $247 \pm 39$   $\mu\text{mol/g}$  aorta,  $P < .0068$  for cholesterol content in total aorta).

**Conclusions** Overexpression of human apo A-I in rabbits inhibits the development of atherosclerosis in this animal model that resembles, in many respects, human atherosclerosis.

**Key Words:** apolipoproteins • atherosclerosis • lipoproteins • cholesterol

## ► Introduction

Accumulation of cholesterol in arterial vessel walls is a prominent feature of atherosclerosis.<sup>1 2 3 4</sup> This accumulation results from unbalanced cholesterol influx and efflux in the vessel wall. HDL and its primary apolipoprotein (apo), apo A-I, are the major serum factors considered to mediate reverse cholesterol transport from the blood vessel wall to the liver. Prospective epidemiological studies in humans<sup>5 6</sup> support the hypothesis that high levels of HDL and apo A-I protect against the progression of atherosclerosis. Badimon et al<sup>7</sup> reported that repeated infusion of human HDL into rabbits fed with cholesterol for 9 weeks resulted in less atherosclerosis compared with controls without HDL infusion. Several studies have shown that overexpression of human apo A-I in specific inbred or genetically engineered strains of mice, natural cholesterol-fed C57BL/6 mice,<sup>8</sup> modified apo E-deficient mice,<sup>9 10</sup> and transgenic mice that express human apo(a)<sup>11</sup> protects against atherogenesis. However, more data from studies with animal models of atherosclerosis that resemble the human disease are required to demonstrate the precise role of apo A-I in limiting the progression of this disease.

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The rabbit has several advantages as an animal model for human atherosclerosis. In rabbits, as in humans, the apo B-containing lipoproteins are the major carriers of cholesterol in plasma.<sup>12</sup> Rabbits, like humans, have cholesteryl ester transfer protein, which plays a central role in the atherosclerotic process.<sup>13</sup> Plasma volumes in rabbits are sufficient to study the metabolism of lipoprotein subclasses and facilitate lipoprotein turnover studies. Furthermore, rabbit atherosclerotic lesions resemble human lesions with respect to the large number of smooth muscle cells, necrotic and acellular lesion cores, extracellular matrix deposition, and occasionally, in older animals, superimposed thrombi.<sup>14 15 16 17 18 19</sup> Also, rabbit aortas can provide sufficient material for detailed study of lipid accumulation, such as the quantification of phospholipid

subclasses.<sup>20</sup> Recently, it has been possible to overcome a major problem in the study of atherosclerotic lesions, the difficulty of noninvasively imaging lesions and following their progression. Ultrasound imaging<sup>21</sup> or serial magnetic resonance imaging<sup>22</sup> can detect lesion fine structure, progression, and complications in rabbits. Finally, considerable genetic variation in lipoprotein levels occurs among rabbits, which may mirror the diverse genetic background in humans.

For these reasons, we have produced human apo A-I-transgenic rabbits.<sup>23</sup> Some of these transgenic rabbit lines expressed high plasma levels of human apo A-I and have elevated HDL cholesterol levels. This new model is useful to further examine the function of human apo A-I in lipid metabolism and in atherosclerosis progression. In the present study, we examined the effect of apo A-I in the rabbit model of atherosclerosis and determined that cholesterol-fed human apo A-I-transgenic rabbits were significantly protected from the development of aortic fatty-streak lesions and lipid accumulation.

## ► Methods

### Animal Model

New Zealand White rabbits transgenic for human apo A-I (line 20)<sup>23</sup> and nontransgenic littermates (age, 3 months; weight, 3.2±0.5 kg) were housed individually in the Charles River Centre (Saint Aubin les Elbeuf, France). We induced atherosclerosis by feeding the animals a cholesterol-rich diet for 14 weeks (all of the diet [120 g per day] was consumed daily). The amount of cholesterol in the diet was adjusted to produce similar plasma levels of cholesterol carried by atherogenic lipoproteins (VLDL and LDL) for the two groups of rabbits. We prepared the atherogenic diet by spraying normal rabbit chow (NIH-09) with cholesterol.

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### Plasma Lipid and Apolipoprotein Analysis

After animals had fasted overnight, blood from the animals was collected into a tube that contained 1 mg/mL Na<sub>2</sub> EDTA, 50 mg/L gentamicin sulfate, and 0.1% sodium azide. Plasma was separated by low-speed centrifugation and kept at 4°C until analysis (<1 week). Human apo A-I was quantified by rocket immunoelectrophoresis with rabbit polyclonal antibodies (SEBIA). Total apo A-I was measured by immunonephelometric assay for which five anti-apo A-I monoclonal antibodies (Diagnostics Pasteur Production) were used.<sup>24</sup> Plasma levels of rabbit apo A-I were calculated by subtraction of human apo A-I from total apo A-I. The reproducibility of apo A-I determinations was assessed from quality-control data. The coefficients of variation between apo A-I assays were 5.8% and 7.4% for human and total apo A-I, respectively. Plasma levels of cholesterol and triglycerides were measured by use of commercially available kits (Boehringer Mannheim). HDL cholesterol levels were determined in plasma after precipitation of apo B-containing lipoproteins by polyethylene glycol-6000.

### Evaluation of Atherosclerosis

Animals were killed by an overdose of intravenous ketamine (80 mg/kg) and carotid exsanguination. The thoracic aorta from the aortic valves to the diaphragm, above the celiac artery, and the abdominal aorta from the diaphragm to the iliac bifurcation were removed and stripped of adventitial fat and tissue. Then, aortas were cut lengthwise into right and left halves by dorsal and ventral incisions. One half of each aorta was fixed in 10% buffered formalin, and the other half was processed for lipid analysis. The fixed aortas were stained with oil red O to reveal fatty deposits. Morphometric assessment of the percentage of the total aorta covered by lipid deposits was determined by computerized planimetry. For light microscopy observations, segments of the oil red O-stained aortas were embedded in paraffin and then stained with hematoxylin-eosin.

### Chemical Analysis of Aortic Wall

Dissected aortas were rinsed in PBS, and the half aortas were extracted with 2:1 (vol/vol) chloroform methanol.<sup>25</sup> The extracted aortic tissues were then lyophilized to obtain a defatted dry weight. Unesterified and esterified cholesterol were determined enzymatically with a fluorometric method.<sup>26</sup> Total phospholipid phosphorus was determined by the Bartlett method.<sup>27</sup>

### In Vitro Cellular Cholesterol Efflux

Cellular cholesterol efflux studies with the Fu5AH rat hepatoma cell line incubated with whole sera were performed by use of the system established by de la Llera Moya et al.<sup>28</sup>

### Statistical Analysis

All data are expressed as mean±SEM. Plasmatic data have been evaluated by use of ANOVA for repeated measures and the Bonferroni test for differences between groups at each time point. For the other data, the Mann-Whitney test was used to establish significance.

## ► Results

### Plasma Lipids and Apolipoproteins

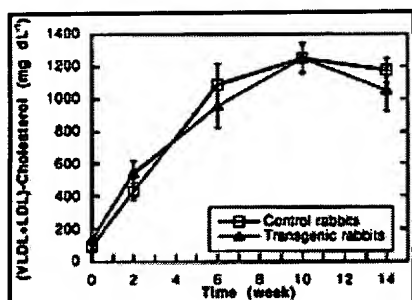
Eight human apo A-I-transgenic and 15 nontransgenic littermate rabbits were fed a cholesterol-rich diet for 14 weeks. Cholesterol in the diet was initially 0.48 g of cholesterol per 120 g of diet but was later adjusted to produce similar levels of non-HDL cholesterol in the plasma of the two groups of rabbits.

Plasma levels of non-HDL cholesterol were evaluated weekly and, after 2 weeks, transgenic and control groups of rabbits consumed 120 g of diet per day supplemented with 0.36 g and 0.48 g of cholesterol, respectively ( $P<.0001$ ), for the remainder of the study. Weight gain was similar on the two diets.

During feeding of these amounts of cholesterol, the levels of non-HDL cholesterol were similar between the two groups (Fig 1▣) and represented 95% of the total plasma cholesterol. At the same time, the level of HDL cholesterol in the transgenic group (Fig 2▣) was almost twice the HDL cholesterol level of the control group (68±11 mg/dL versus 37±3 mg/dL for values at 14

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weeks;  $P < .001$ ). Cholesterol distribution between VLDL and LDL was similar for the two groups. Endogenous rabbit apo A-I and human apo A-I plasma levels during the experiment were determined in the two groups (Fig 3A). The total (human plus rabbit) apo A-I plasma level was threefold higher in the transgenic group compared with the control group. The variation in level of total apo A-I over time in response to the cholesterol diet was similar between transgenic and control rabbits (Fig 3A). In transgenic rabbits, at the beginning of the diet, human apo A-I decreased rapidly while rabbit apo A-I increased (Fig 3B). A similar inverse variation of rabbit and human apo A-I was observed previously in transgenic rabbits.<sup>23</sup> When data from the two groups were pooled, the HDL cholesterol levels correlated with total apo A-I levels ( $P < .0005$ ). For the transgenic group, HDL cholesterol levels (week 14) correlated with total apo A-I ( $P < .0017$ ) and human apo A-I ( $P < .0018$ ) levels.

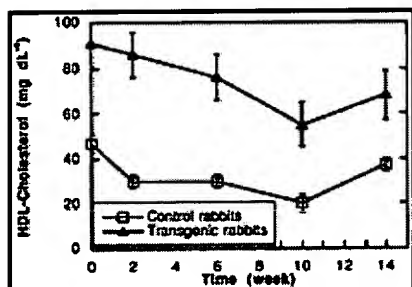


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**Figure 1.** Cholesterol plasma levels of apolipoprotein B-containing lipoproteins (VLDL+LDL) during feeding of the cholesterol-supplemented diet. Values are expressed as milligram per deciliter. There were no statistical differences between the VLDL+LDL plasma cholesterol levels in the transgenic ( $n=8$ ) and control ( $n=15$ ) groups (no group effect; no interaction between groups and times; time effect,  $P < .001$ , but no differences between the two groups for each time point).



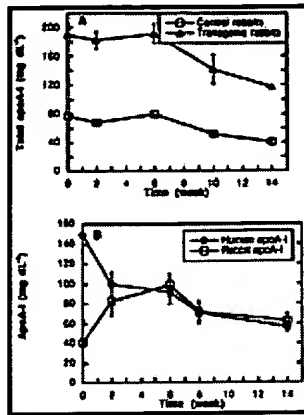
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**Figure 2.** Cholesterol plasma levels of the HDL fraction during the diet. Values are expressed as milligram per deciliter. HDL cholesterol values were twofold to threefold higher in the transgenic ( $n=8$ ) group than in the control ( $n=15$ ) group (group and time effect,  $P < .001$  and  $P < .001$ , respectively;  $P < .001$  for differences between the two groups at each time point).

**Figure 3.** Apolipoprotein A-I (apoA-I) plasma levels during the diet. Values are expressed as milligram per deciliter. A, Plasma levels of total apoA-I for control ( $n=15$ ) and transgenic ( $n=8$ ) rabbits (group and time effect,  $P < .001$  and  $P < .001$ , respectively; significant differences between the two groups for

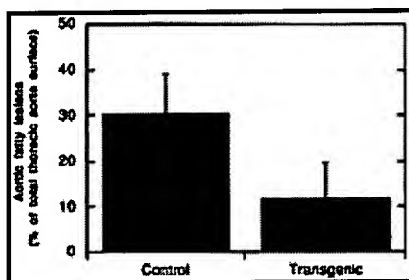


each time point,  $P<.001$ ). B, Endogenous rabbit and human plasma levels of apoA-I for transgenic rabbits ( $n=8$ ;  $P<.001$  for differences between groups at baseline; no differences at other time points).

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### Morphological and Histological Analysis

Thoracic and abdominal aortas were stained with oil red O. The control group had  $30\pm 8\%$  of the thoracic aorta surface covered by lesions, whereas only  $15\pm 12\%$  (50% of control;  $P<.0027$ ) of the thoracic aorta surface of transgenic rabbits was covered by lesions (Fig 4). Similar results were observed for the abdominal aortas. Histological examination of the aortas of the two groups of rabbits revealed similar lesions characterized by a large accumulation of macrophage foam cells and some smooth muscle cells in the intima.



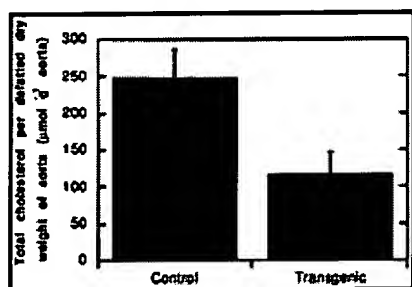
**Figure 4.** Atherosclerosis involvement in thoracic aorta. Values are expressed as percent of aortic surface covered by fatty streaks ( $P<.0027$ , transgenic [ $n=8$ ] vs control [ $n=15$ ] groups).

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### Lipid Accumulation in the Aortic Wall

To analyze lipid accumulation, a chemical analysis of the lipids extracted from the aortic wall was performed. The amount of total cholesterol per gram of defatted dry weight of total aorta in the transgenic group (Fig 5) was 47% that of the control group ( $116\pm 31$  versus  $247\pm 39$   $\mu\text{mol/g}$  aorta;  $P<.0068$ ). This reflected a reduced accumulation of cholesteryl ester in the transgenic group that was 38% the level of the control group ( $66\pm 22$  versus  $172\pm 29$   $\mu\text{mol/g}$  aorta;  $P<.0023$ ) as well as a lower accumulation of unesterified cholesterol in the transgenic group that was 64%

the level of the control group ( $48 \pm 9$  versus  $74 \pm 9$   $\mu\text{mol/g}$  aorta;  $P < .05$ ). The cholesteryl ester content in the total aorta corresponded to  $67.3 \pm 1.5\%$  of total cholesterol for the control group and  $46.7 \pm 6.8\%$  of total cholesterol for the transgenic group (69% of control;  $P < .0001$ ). In addition, the phospholipid accumulation per gram of defatted dry weight of total aorta was also reduced in the transgenic group, to 80% of control ( $39 \pm 2$  versus  $49 \pm 3$   $\mu\text{mol/g}$  aorta;  $P < .0225$ ).



**Figure 5.** Total cholesterol accumulation in entire aorta. Values are expressed as micromoles per gram of defatted dry weight of total aorta ( $P < .0068$ , transgenic [ $n=8$ ] vs control [ $n=15$ ] groups).

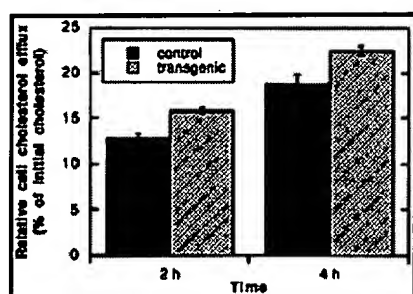
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### Cellular Cholesterol Efflux

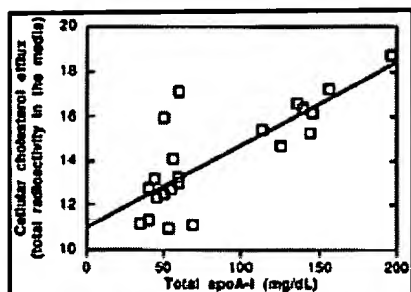
To determine the potential mechanism of atherosclerosis protection in transgenic rabbits, the efflux of labeled cholesterol from Fu5AH cells exposed to 5% diluted serum from transgenic and control rabbits (after 14 weeks of atherogenic diet) was determined. All serum samples promoted cholesterol efflux. However, mean cholesterol efflux promoted by the incubation of serum samples from the transgenic group (Fig 6) was significantly higher than that from the control group (+24.5% of control value at 2 hours and +20.2% of control value at 4 hours;  $P < .0001$ ). The relationships between cholesterol efflux and non-HDL cholesterol levels, HDL cholesterol levels, and concentration of total or human apo A-I levels were analyzed. No correlation was found between cholesterol efflux and non-HDL cholesterol. When data from the two groups were pooled, cholesterol efflux correlated with total apo A-I levels at 2 ( $P < .0005$ ; Fig 7) and 4 hours ( $P < .013$ ) of incubation and with HDL cholesterol levels at 2 ( $P < .01$ ) and 4 hours ( $P < .05$ ) of incubation. For the transgenic group, cholesterol efflux correlated with total apo A-I levels at 2 hours ( $P < .043$ ).



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**Figure 6.** Relative cholesterol efflux. Serum from transgenic and control rabbits was incubated with cholesterol-enriched Fu5AH cells, and cholesterol efflux by the cells was measured after 2 and 4 hours of incubation at  $37^\circ\text{C}$ . Values are expressed as percent of initial cholesterol present in the cells that was found in the medium after incubation. Values are the mean of relative cholesterol efflux promoted by the incubation of serum from control ( $n=15$ ) or transgenic ( $n=8$ ) rabbits.

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**Figure 7.** Relation between cellular cholesterol efflux and total apolipoprotein A-I (apo A-I) plasma levels for transgenic (n=8) and control (n=15) rabbits. Cellular cholesterol efflux at 2 hours was highly correlated with total apo A-I plasma levels ( $r=.806$ ,  $P<.0005$ ).

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## ► Discussion

Our results demonstrate the protective effect of apo A-I in an animal model of atherosclerosis that resembles human atherosclerosis in many respects. We found that overexpression of human apo A-I in cholesterol-fed transgenic rabbits significantly inhibited the development of aortic fatty-streak lesions and lipid accumulation. In addition, at least one mechanism by which apo A-I and HDL may act to prevent atherosclerosis progression in this model was suggested from the results: enhancement of reverse cholesterol transport.

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Surprisingly, in a preliminary experiment, we observed that transgenic animals developed a higher degree of hypercholesterolemia than control rabbits in response to 1% (wt/wt) cholesterol in their diet. The higher degree of hypercholesterolemia in transgenic rabbits was compatible with an inhibition of hepatic lipase by apo A-I as described previously.<sup>29 30 31 32</sup> Transgenic rabbits fed an unsupplemented chow diet showed cholesterol levels of atherogenic lipoproteins similar to levels in transgenic rabbits.<sup>23</sup> Hepatic lipase activity varies widely between species. It is high in humans and rats and very low in rabbits (15% of human hepatic lipase activity).<sup>32 33 34</sup> Therefore, enhancement of hypercholesterolemia in the apo A-I-transgenic rabbits may reflect the combined effect of high plasma levels of human apo A-I and low levels of hepatic lipase in rabbits. To evaluate the effect of the apo A-I transgene on atherosclerosis development, it was necessary to adjust the level of cholesterol in the diet to produce the same level of non-HDL cholesterol in the plasma of the transgenic and nontransgenic groups of rabbits. Such a technique was used previously to reduce variation in groups of animals in which large genetic diversity occurs. In view of the prospect of human gene therapy for atherosclerotic vascular disease by production of high plasma levels of apo A-I, it will be important to assess further the mechanism



of apo A-I-induced hypercholesterolemia.

Dramatic inhibition of diet-induced atheroma was demonstrated in the apo A-I-transgenic rabbits. Lipid accumulation and lesion area were reduced  $\approx 50\%$  in the aortas of transgenic rabbits compared with control rabbits. Many factors have been proposed as important for the development of atherosclerotic lesions. The results of the present study suggest that apo A-I is very effective in correcting the imbalance of factors that determine the rate of atherogenesis. Because there were no differences in plasma cholesterol levels in the fractions of apo B-containing lipoproteins between the two groups of rabbits, the effect of the human apo A-I transgene on atherosclerosis must be related to the higher levels of HDL cholesterol and apo A-I in the plasma of the transgenic animals.

An abundance of data that confirm the inverse relation between HDL and atherosclerotic vascular disease has been reported.<sup>5 6</sup> Studies in culture systems<sup>35 36</sup> supported the hypothesis that apo A-I-containing lipoproteins exert a beneficial effect against development of atherosclerosis. Such studies indicated that HDL facilitates reverse cholesterol transport, during which cholesterol is transported away from cells of extrahepatic tissues and carried back to the liver, where it can be eliminated or reused. Although other mechanisms have been proposed for the antiatherosclerotic effect of HDL, the present in vitro cellular cholesterol efflux studies strongly support the hypothesis that HDL-rich plasma stimulates reverse cholesterol transport. The Fu5AH cell culture system was previously used to evaluate the potential of sera to promote cellular cholesterol efflux.<sup>24</sup> In agreement with the data reported with human sera, there was no correlation between cholesterol efflux and the content of apo B-containing lipoproteins in serum samples. Although apo B-containing lipoproteins can enrich Fu5AH cells with cholesterol, these lipoproteins do not appear to affect the rate of removal of cholesterol from Fu5AH cells. On the other hand, the highest correlation with cholesterol efflux was found with HDL cholesterol and total apo A-I plasma levels. Moreover, cholesterol efflux was higher when Fu5AH cells were incubated with sera from transgenic versus control rabbits. In a report that described the human apo A-I-transgenic rabbit line,<sup>23</sup> we described the presence of a large amount of apo A-I-containing lipoproteins with pre- $\beta$  mobility. These particles are considered the primary acceptor of cholesterol efflux from the plasma membrane,<sup>37</sup> and their plasma levels were correlated with cholesterol efflux.<sup>23</sup> HDL promotes cholesterol efflux from cholesterol-enriched human monocyte-derived macrophages<sup>38</sup> and also limits cholesterol accumulation in these cells during cholesterol enrichment. Therefore, it is likely that HDL can limit cholesterol accumulation in cells even as these cells are accumulating cholesterol.

The present study demonstrated that human apo A-I produced in the liver of transgenic rabbits enhanced reverse cholesterol transport and protected the aorta from diet-induced atherosclerosis, despite similar levels of atherogenic lipoproteins in the plasma of the transgenic and control rabbits. The rabbit is a good animal model for human atherosclerosis and is well suited for many types of studies. The data generated from this model will enhance our understanding of the role of apo A-I in protecting against the development of atherosclerosis.

## ► Acknowledgments

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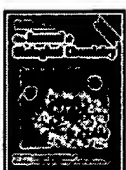
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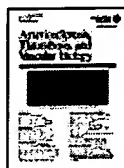
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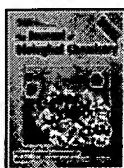
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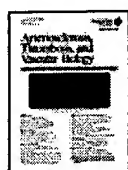
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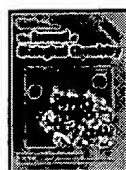
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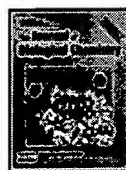
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